

Effects of a combined progressive resistance training and functional electrical stimulation-evoked cycling exercise on lower limb muscle strength of individuals with incomplete spinal cord injury: A randomized controlled study

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ABSTRACT

Objectives: This study was conducted to investigate the effects of combined progressive resistance training (PRT) and functional electrical stimulation-evoked leg cycling exercise (FES-LCE) on isometric peak torque and muscle volume in individuals with incomplete spinal cord injury.

Patients and methods: In the single-blind, randomized controlled trial performed between April 2015 and August 2016, 28 participants were randomized between two exercise interventions (FES-LCE+PRT and FES-LCE alone), and training was conducted over 12 weeks. The isometric muscle peak torque and muscle volume for both lower limbs were measured at the baseline and after 6 and 12 weeks. Linear mixed-model analysis of variance was performed to test the effects of FES-LCE+PRT versus FES-LCE on each outcome measure over time via an intention-to-treat analysis.

Results: Twenty-three participants (18 males, 5 females; mean age: 33.4±9.7 years; range 21 to 50 years) completed study (10 in the FES-LCE+PRT group, and 13 in the FES-LCE group). The 12-week pre- and posttraining change for left hamstrings' muscle peak torque in the FES-LCE+PRT group (mean difference=4.5±7.9 Nm, 45% change, p<0.05) was consistently higher than that in the FES-LCE group (mean difference=2.4±10.3 Nm, 4% change; p<0.018). The improvement in the right quadriceps muscle's peak torque of the FES-LCE+PRT group (mean difference=19±7.6 Nm, 31% change, p<0.05) was more significant compared to the FES-LCE group. The left muscle volume showed a remarkable increase after 12 weeks in the FES-LCE+PRT group (mean difference=0.3±9.3 L, 7% change, p<0.05).

Conclusion: The combination of PRT and FES-LCE was better in improving lower limb muscle strength and volume in chronic incomplete individuals with spinal cord injury.

Keywords: Electrical stimulation, ergometry, muscle strength, resistance training, spinal cord injuries.

Motor-incomplete spinal cord injury (SCI) is a disability that may reduce lower limb motor function and limit an individual's quality of life due

to immobility or loss of bowel and bladder control.^[1] Individuals with significant muscle disturbance below their neurological level of SCI will rapidly progress

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to atrophy^[2] and develop low fatigue resistance.^[3] Gorgey and Dudley^[4] showed that the musculature of individuals with incomplete SCI atrophied by 10% after three months and progressed to a remarkable muscle loss four to five months after injury. The consequences of incomplete SCI not only aggravate the physical function but also develop into other complications that are directly related to high hospitalization rates and increased care costs.^[5]

Regaining lower limb muscle strength and volume is beneficial for an individual with incomplete SCI as it improves over-ground walking and performance of daily living activities to a higher quality.^[6] The gastrocnemius and tibialis anterior muscles play an essential role in stability during standing and walking.^[7,8] Progressive resistance training (PRT) with superimposed electrical stimulation resulted in improvement in quadriceps muscle strength after eight weeks of training.^[9] Thus, further findings on the other lower limb muscles (e.g., hamstrings, gastrocnemius, and tibialis anterior) are necessary. Progressive resistance training alone may be insufficient to elicit further improvement of these muscles since they respond to strength training but are not adequately overloaded.^[10]

Functional electrical stimulation (FES)-evoked leg cycling exercise (LCE) is a technique that can improve lower limb muscle strength^[11-13] and size^[14-16] among individuals with SCI. To date, no study on incomplete SCI alone has been conducted; thus, PRT may be combined with FES-LCE to enhance the dose potency of strength training. Given that the effects of the combination of FES-LCE and PRT among individuals with incomplete SCI have been inconclusive, the current study sought to investigate whether (i) muscle strength of the quadriceps, hamstrings, tibialis anterior, and gastrocnemius improves and (ii) lower limb muscle volume increases after 12 weeks of FES-LCE+PRT among individuals with incomplete SCI compared to FES-LCE training alone. We hypothesized that 12 weeks of training (FES-LCE+PRT) would improve the lower limb muscle strength and volume compared to FES-LCE alone.

PATIENTS AND METHODS

In the single-blind, randomized controlled trial, a total of 28 individuals with incomplete SCIs were recruited from the University Malaya Medical Centre, Kuala Lumpur. They were recruited by a rehabilitation physician following the inclusion criteria: having an American Spinal Injury Association Impairment Scale

(AIS) grade of C or D for more than 24 months, the presence of an injury between the levels C4 and T12, possessing at least 90° knee range of motion (able to cycle) with at least one-fifth in manual muscle testing of the tibialis anterior and gastrocnemius muscles, and being responsive to electrical stimulation (moderate weakness was defined as three-fifth or four-fifth on manual muscle testing). Individuals with a recent history of trauma or metal implants in lower limbs, infected skin pressure ulcers on weight-bearing areas, uncontrolled spasticity or pain, uncontrolled autonomic dysreflexia, or a history of cardiovascular and cardiorespiratory issues were excluded.

This study contained a parallel-group randomized assignment that involved individuals with incomplete SCI. Participants were recruited for the study in April 2015 using a simple random sampling strategy, and the last participant completed their follow-up assignments in August 2016.

The participants were randomly assigned all at once based on their names and allocated into the FES-LCE+PRT or FES-LCE groups by a blinded casual research assistant using coin toss methodology. The research assistant was not involved in the study, and the participants' personal details were then concealed in opaque sealed envelopes and kept in a locked drawer. The envelopes could only be accessed by the researcher for the baseline assessments and training program schedule. A safety kit was provided for any emergency.

Outcome measures

The physical characteristics of all participants, such as age, sex, height, body weight, body mass index, and medical history (e.g., AIS grade, level of injury, and period of injury), were collected from hospital medical records (with permission from the department and informed consent of the participants). This study's primary outcomes were the isometric muscle peak torque for the quadriceps and hamstring muscles and the muscle volume for lower limbs. The secondary outcome was the isometric muscle peak torque for the tibialis anterior and gastrocnemius. All outcomes were assessed at baseline, on the first session at six weeks, and on the first session at 12 weeks of training.

The isometric testing technique during the three assessment periods was based on the Biodex Medical Systems application/operation manual (Biodex Medical Systems Inc., Shirley, NY, USA). The maximum muscle strength was obtained from the highest voluntary peak torque (Nm) of every muscle

contraction for data analyses. No neurostimulation was administered during the assessment. For the quadriceps and hamstring muscles, the participants were tested in a seated position (hip and knee at 90°), with their thighs and chests strapped and their arms crossed over their chest. For the tibialis anterior and gastrocnemius muscles, the setup was changed as the knee was held at 20 to 30° of flexion with the footplate at a neutral position (0°). All muscles were assessed over a 4 sec isometric contraction, followed by 30 sec of recovery; this process was repeated three times.

The muscle volume (L) was assessed in the supine posture for the lower limbs, with each lower limb divided into six imaginary cones, as described by Heesterbeek et al.^[17] The measurement was made based on the circumference (C) and height (H) of each cone through the following formula:

$$\text{Volume cone (L)} = 1/12\pi \times H \times (C_{\text{upper}}^2 + (C_{\text{upper}} \times C_{\text{lower}}) + C_{\text{lower}}^2).$$

The circumference landmarks were based on the upper leg, which is one third of the distance from the upper leg to midpatellar, suprapatellar, midpatellar, subpatellar, maximum calf, and minimal ankle. The height was between the adjacent circumferences. The landmarks were marked according to each participant so that the measurement was consistent in every assessment. The measurements were made multiple times to ensure an element of rigor. All cones were summed together to obtain the ankle-to-thigh muscle volume.

Exercise training program

The participants could not be blinded to their group allocation since no placebo intervention existed in this study. However, the physicians and the primary research assistant were blinded to the group allocation. The participants were advised about the underlying exercise protocol before starting their training program. The participants underwent familiarization and practice training in their first session. Adherence was determined by the number of sessions that the participants completed as more than 80% of the planned exercise sessions, and compliance was quantified from the elements within the exercise sessions' requirements. The FES-LCE+PRT group underwent 24 FES-LCE and 12 PRT sessions over 12 weeks, comprising two sessions of FES-LCE and one session of PRT each week. The FES-LCE group received 36 FES-LCE sessions over 12 weeks (three sessions per week). Chronic SCI was recommended to undergo at least 20 min of aerobic

exercise with three sets of moderate to vigorous strengthening to each major functioning muscle twice a week for fitness and health benefits.^[18] Using this exercise prescription, we sought to minimize exercise risks for those with chronic SCI who had not been exercising for a long time;^[18] therefore, we chose not to deploy high-intensity interval training or similar high-impact aerobic activities.

The participants were advised to wear exercise attire, eat 1 h before the session, and perform urinary catheterization before attending their training sessions. Self-adhesive electroconductive gel electrodes (HASOMED GmbH, Magdeburg, Germany) were placed on the skin over the corresponding muscle groups on both legs for transcutaneous neuromuscular stimulation. Large stimulation electrodes (13.0×7.5 cm) and small stimulation electrodes (5.0×9.0 cm) were used to activate the muscles. For quadriceps muscles, one electrode was placed over the vastus medialis muscle (2 to 3 cm above the superior aspect of the patella), and the other was placed over the vastus lateralis (lateral to and 30 cm above the patella). For the hamstrings, one electrode was placed 2 to 3 cm above the popliteal fossa and the other 30 cm above the popliteal fossa. For the tibialis anterior and gastrocnemius muscles, the electrode (size 5.0×9.0 cm) was placed above and below the respective muscle bellies. Electrode sites were marked with indelible ink for site replication between sessions.

Each FES-LCE session lasted for 1 h. The participants used a motorized cycle ergometer (Viva 2 Parkinson; MOTomed, Reck, Germany) that was synchronized with a Hasomed RehaStim FES system (RehaStim2; Hasomed GmbH, Magdeburg, Germany). During the first 5 min, the participants performed a warm-up (without electrical stimulation) with assisted passive movements of the pedal by the ergometer motor to reduce any reactive spasms that might occur upon initiation of movement. Neurostimulation intensity was automatically started by the RehaStim system connected to the MOTomed cycle ergometer. The neurostimulation parameters were a pulse width of 300 µsec, pulse frequency of 30 Hz, cycling speed of 35 revolutions (rev)/min, and current amplitude range of 70 to 140 mA. The participants were asked to cycle voluntarily for 50 min, and the current amplitude of FES was increased based on their tolerance every 10 min.

The participants' cycling speed was set to a target cadence of 35 rev/min. The participants' pedaling cadence was held constant and maintained at not less

than 35 rev/min by the ergometer motor. Exercise tolerance and relative exercise intensity were assessed using the 20-point Borg Perceived Exertion Scale. The participants were requested to maintain an exercise intensity of 15 to 18 on the scale. The resistance was manually adjusted and increased by 1 W when exceeding 35 rev/min. The distances covered in active and passive exercise, duration of active and inactive exercise, and the power output were recorded during each session.

Neurostimulation was also applied to all muscles for assistance during PRT, and the parameters and electrode placements were similar to those for FES-LCE. Progressive resistance training for knee flexion, extension, dorsiflexion, and plantarflexion was conducted using a Biodex Isokinetic System (version 3; Biodex Medical Systems, Shirley, NY, USA) that was synchronized with the RehaStim portable FES system. The seated body position during training was identical to the standard leg strength assessments on the Biodex Isokinetic System. The isokinetic mode was used for this study as it allowed considerable muscle recruitment during training. Before starting PRT, each participant underwent a trial session (at baseline, six weeks, and 10 weeks) to select the optimal resistance during training using the 10 repetitive maximum

(RM) protocol. During the first six weeks, all muscles' weight was 50% of 10 RM, with three to four sets of 10 repetitions and a 5 to 10-sec recovery between each repetition. The weight progressed to 70% of 10 RM after six weeks and 100% of 10 RM after 10 weeks. However, if the participants were able to successfully complete the PRT, then 10 RM was reassessed, and they were trained based on the new machine resistance.

Statistical analysis

The sample size was calculated using the G*Power version 3.0 software (Heinrich-Heine-Universität, Düsseldorf, Düsseldorf Germany). The calculation was based on a clinical trial study^[9] wherein 28 participants could provide 80% power in detecting a between-group difference equivalent to 15% of the mean baseline for isometric muscle peak torque with a risk of a type 1 error of 0.05 and an effect size of 0.25. Data were analyzed using IBM SPSS version 21.0 software (IBM Corp., Armonk, NY, USA). The Shapiro-Wilk test and a box plot were used to assess the normality of the variables. Linear mixed model analysis of variance was performed to test the effects of FES-LCE+PRT versus FES-LCE on each outcome measure over time via an intention-to-treat analysis (all subjects randomized to the study were included for analysis). Those who had

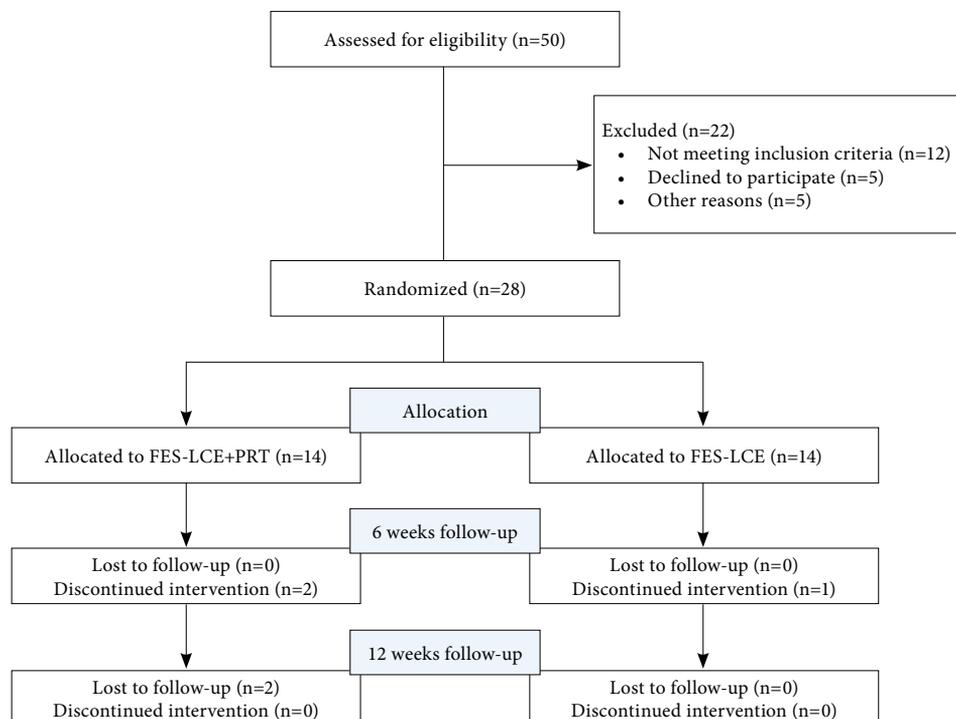


Figure 1. Experimental design of the investigation.

FES: Functional electrical stimulation; LCE: Lower cycling exercise; PRT: Progressive resistance training.

been enrolled in this study were analyzed to which group they were randomized. A p value of <0.05 was considered statistically significant.

RESULTS

Among the 28 participants, 23 (18 males, 5 females; mean age: 33.4 ± 9.7 years; range 21 to 50 years) completed the training and returned for their final assessment (Figure 1). Ten of these participants were in the FES-LCE+PRT group, and 13 were in the FES-LCE group. The main reasons for dropout were illness (three in the FES-LCE+PRT group) and lack of adherence (one in the FES-LCE+PRT group and one in the FES-LCE group) to the training. The physical characteristics, medical history, and injury characteristics of the participants are presented in Table 1. No severe adverse events were observed during baseline assessment or training. All data were normally distributed (Shapiro-Wilk analysis; Figure 1). The participants in the FES-LCE group completed 87% of the cycling sessions, whereas those in the FES-LCE+PRT group completed 96% of the cycling sessions and 94% of the PRT sessions. Both groups met their duration compliance by completing 50 min of FES-LCE each session. The FES-LCE+PRT group also completed the entire PRT regime.

Tables 2 and 3 show the effect of FES-LCE+PRT versus FES-LCE on the muscle peak torque and muscle volume for the right and left lower limbs, respectively. No significant differences were detected between groups on the left quadriceps, tibialis anterior, or gastrocnemius muscle peak torque; considerable to significant differences were noted in the peak torque of the right quadriceps and gastrocnemius muscles (Table 2). The isometric muscle peak torques within the left quadriceps (mean difference= 14.9 ± 2.2 Nm, $p=0.001$), hamstring (mean difference= 4.5 ± 0.9 Nm, $p=0.011$), tibialis anterior (mean difference= 3.2 ± 6.8 Nm, $p=0.029$), and gastrocnemius muscles (mean difference= 4 ± 4.6 Nm, $p=0.007$) in the FES-LCE+PRT group were consistently higher than those in the FES-LCE group. Moreover, the FES-LCE+PRT group showed a clinically relevant improvement in the isometric muscle peak torque of the right quadriceps (mean difference= 19 ± 4.8 Nm, $p=0.002$), hamstrings (mean difference= 4.4 ± 3.5 Nm, $p=0.003$), and tibialis anterior (mean difference= 0.5 ± 0.8 Nm, $p=0.018$) muscles. However, this improvement was not significantly different between the groups ($p>0.05$, Table 2). We found that the percentage for a dominant right side was 74% of 23 participants. A strong effect

TABLE 1
Demographic and injury characteristics

Characteristics	FES-LCE+PRT group (n=10)			FES-LCE group (n=13)		
	n	%	Mean±SD	n	%	Mean±SD
Mean age (year)			33.4±9.7			38.8±8.4
Mean height (cm)			168.7±6.8			169.6±7.7
Sex						
Male	8	80		10	77	
Female	2	20		3	23	
Mean weight (kg)			65.4±11.1			62.6±10.4
Motor level (%)						
T3-T6	4	40		4	30.8	
T12-L1	6	60		9	69.2	
LEMS						
MMT over 3/5 (%)	80			38		
Quadriceps	70			38		
Hamstring	60			31		
Tibialis anterior gastrocnemius	80			31		
Time since injury (year)			7.4±2.7			8.4±4.2
AIS C			3.0±30.0			8.0±61.5
AIS D			7.0±70.0			5.0±38.5

FES: Functional electrical stimulation; LCE: Lower cycling exercise; PRT: Progressive resistance training; SD: Standard deviation; L: Lumbar; T: Thoracic; LEMS: Lower extremity muscle strength; MMT: Manual muscle strength; AIS: American Spinal Injury Association Impairment Scale.

TABLE 2
Isometric muscle peak torques (Nm) in the FES-LCE+PRT and FES-LCE groups

Outcome measure	FES-LCE group				FES-LCE+PRT group				Between group				
	Baseline Mean±SD	6 Weeks		12 weeks		Baseline Mean±SD	6 Weeks		12 weeks		p	95% CI	Partial Eta Square
		Mean	95% CI	Mean	95% CI		Mean	95% CI	Mean	95% CI			
Left muscle peak torque (Nm)													
Quadriceps	48.3±58.0	50.8	15.3-73.3	52.3	16.6-74.6	52.3±48.7	57.9	24.9-90.9	67.2	34.0-100.3	0.097	39.3-66.4	0.82
Hamstrings	6.1±7.9	8.2	1.8-12.6	8.5	2.2-12.9	10.1±10.3	12.3	6.5-18.9	14.5	8.4-20.6	0.018*	7.2-11.8	0.97
Tibialis anterior	1.9±3.4	1.0	-1.2-2.9	1.1	-2.6-4.5	1.4±2.7	2.6	0.3-5.0	4.6	0.6-8.9	0.330	0.8-3.1	0.45
Gastrocnemius	9.3±12.4	11.6	0.2-19.5	13.1	1.0-29.5	13.1±17.8	15.4	4.4-26.4	17.1	6.0-29.5	0.096	8.0-16.1	0.82
Right muscle peak torque (Nm)													
Quadriceps	50.1±57.6	54	11.9-82.1	55.7	12.8-84.5	61.4±69.3	67	26.9-107.0	80.4	39.4-121.2	0.056	45.0-78.2	0.89
Hamstrings	17.8±23.6	18.4	4.2-27.2	19.5	4.2-29.0	14.4±17.3	15.2	3.1-29.4	18.8	4.7-33.0	0.123	12.0-23.0	0.77
Tibialis anterior	6.6±12.0	3.6	0.4-5.7	3.3	0.3-5.2	1.7±3.6	2.2	-7.4-5.3	2.2	-0.6-27.1	0.192	1.6-4.9	0.65
Gastrocnemius	15.7±22.2	19.6	3.8-29.4	17.7	2.9-27.2	14.0±18.5	15.4	0.8-30.0	13.2	6.8-27.1	0.060	10.3-21.6	0.89

FES: Functional electrical stimulation; LCE: Lower cycling exercise; PRT: Progressive resistance training; SD: Standard deviation; CI: Confidence interval; Nm: Newton meter; * p<0.05.

TABLE 3
Muscle volumes (L) in the FES-LCE+PRT and FES-LCE groups

Outcome measure	FES-LCE group				FES-LCE+PRT group				Between group				
	Baseline Mean±SD	6 Weeks		12 weeks		Baseline Mean±SD	6 Weeks		12 weeks		p	95% CI	Partial Eta Square
		Mean	95% CI	Mean	95% CI		Mean	95% CI	Mean	95% CI			
Muscle volume (L)													
Left	5.4±0.3	5.6	5.4-5.7	5.7	5.4-5.7	5.6±0.3	5.7	5.5-6.0	6	5.8-6.2	0.005*	5.6-5.7	0.9
Right	5.5±0.4	5.6	5.3-5.8	5.7	5.5-6.0	5.5±0.4	5.7	5.5-6.0	5.9	5.6-6.1	0.21	5.5-5.7	0.6

FES: Functional electrical stimulation; LCE: Lower cycling exercise; PRT: Progressive resistance training; SD: Standard deviation; CI: Confidence interval; * p<0.05.

was also observed on the left muscle volume, which showed 90% variance ($p < 0.05$) with a mean difference of 0.3 L after 12 weeks of FES-LCE+PRT.

DISCUSSION

This study sought to compare the effect of FES-LCE+PRT versus FES-LCE only on the isometric muscle peak torques and muscle volumes. Primarily, our findings revealed an improvement in the lower limb muscle peak torque after 12 weeks of training with FES-LCE+PRT. The means of the muscle peak torque and volume in the FES-LCE+PRT group were higher than those in the FES-LCE group. This work was the first to investigate the effect of the combination of FES-LCE and PRT versus FES-LCE alone. In a previous study, the researchers discovered the effectiveness of PRT compared to isometric contraction alone.^[9] In their study, the training program was conducted three times per week for eight weeks. In this study, resistance training was conducted once a week. We believe that two to three times a week of PRT and FES-LCE can significantly affect the muscle strength and volume of the lower limbs.

Functional electrical stimulation-evoked leg cycling exercise has been utilized in many types of exercise regimes that can alter the muscle fiber types from fast-twitch muscles to slow-twitch muscles,^[19,20] change the composition of myosin heavy chain,^[19,21] and improve the oxidative enzyme concentration.^[3] With the help of PRT, FES-LCE can enhance muscle strength and muscle volume, total energy expenditure, and general health among individuals with SCI, thereby decreasing the risk of type 2 diabetes mellitus and cardiovascular disease incidence.^[22]

In the present study, isometric muscle peak torque was suitable for chronic SCI since most participants did not have a full lower limb range of motion. At the same time, muscle volume was determined using a measuring tape as it is affordable and easy to use. However, change in muscle volume can be a crude measurement since hydration and carbohydrate intake were not controlled in our work. In future studies, dietary control should be monitored to obtain a significant measurement.

Unfortunately, the tibialis anterior muscle in the present study failed to gain strength after 12 weeks of training with FES-LCE and PRT, possibly because the muscle did not produce sufficient significant stimulus to evoke the necessary adaptation.^[23] For example, the ankle had limited dorsiflexion movement during

FES-LCE and PRT due to the restricted movement of the pedal in the FES and Biodex machines. However, the optimal angle to stimulate the tibialis anterior and evoke maximal ankle excursions during FES was not investigated.

A significant improvement was observed in muscle volume. The increment was 7% in the intervention group and 3% in the control group. Shields and Dudley-Javoroski^[23] revealed that the soleus muscle mass gains rapid and prolonged improvement only after one year of training with electrical stimulation. They also showed that the load applied to the muscle being trained is minimal, and thus, it may not be sufficient enough to attribute increases to torque in training. In this study, however, we observed an increase in muscle volume in only three months of training with PRT and FES-LCE training.

There was a higher proportion of AIS Grade D patients in the FES-LCE+PRT group than in the FES-LCE group. The difference was not much, but it could affect the result. AIS Grade D patients preserved at least half of the key muscle that could generate movement,^[24] which might increase the descending neural drive to the muscle and improve the axonal action potential reaching the muscle from the spinal cord.

The present study has several limitations. First, the sample size is small, and the author did not consider accounting for dropout, which decreased the study's power. Second, the functional tasks and quality of life were not measured in this study. Thus, future studies may provide an improved understanding of the effect of the current intervention. This study can serve as a basis for future studies and may add to the growing body of literature on the clinical efficacy of FES-LCE+PRT on other outcome measures.

In conclusion, the combination of FES-LCE and PRT led to a remarkable improvement in muscle strength and volume amongst individuals with incomplete SCI. The combination of exercises with PRT-FES might provide better improvement. This study can serve as a basis for future studies and may add to the growing body of literature on the clinical efficacy of FES-LCE+PRT on other outcome measures and conditions.

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Ethics Committee Approval: The study protocol was approved by the Universiti Malaya Ethics Committee (date/no: 20161-2097). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Gathering data, writing the manuscript: H.R.; Conceptual framework: N.H.; Data analysis: N.A.H.; Revising the manuscript: H.M.

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